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ORIGINAL ARTICLE

# Treatment beyond progression in metastatic colorectal cancer: to double or not to double the dose of bevacizumab?

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## *Summary*

***Purpose:*** *Bevacizumab or cetuximab represent the standard treatment in association with classical chemotherapy in confirmed metastatic colorectal cancer (mCRC). Bevacizumab could be continued after the first disease progression with an overall survival (OS) advantage, compared to chemotherapy alone, but the optimal dose remains a debatable issue.*

***Methods:*** *In a retrospective analysis of mCRC patients treated with bevacizumab, we selected patients with administration beyond progression, and stratified them according to the dose received– same dose bevacizumab (SDB) as first-line chemotherapy or double dose bevacizumab (DDB). For each group we evaluated OS, time to treatment failure (TTF) and progression-free survival in the first-line (PFS1) and in the second-line (PFS2).*

***Results:*** *In the first-line therapy, oxaliplatin backbone regimen was used in 73% SDB, compared with 22.5% DDB patients, while irinotecan was used in 75% DDB and 27% SDB patients. Second-line oxaliplatin was given to 50% DDB and 29.7% SDB patients, while irinotecan was administered to 47.5% DDB and 70.3% SDB patients. The median values were: OS - 41 months in the DDB group and 25 months in the SDB group (p = 0.01); TTF - 24 months in the DDB group and 19 months in the SDB group (p=0.009); PFS1 - 17 months in the DDB group and 12 months in the SDB group (p=0.008); PFS2 - 9 months in the DDB group and 5 months in the SDB group (p = 0.03).*

***Conclusions:*** *Doubling the dose of bevacizumab at progression seems to provide OS and PFS advantage for mCRC patients.*

***Key words:*** *colorectal, cancer, progression, bevacizumab, metastasis*

## Introduction

Colorectal cancer (CRC) represents one of the most frequent types of cancer worldwide. In September 2018 GLOBOCAN approximates the number of new cases at 1,850,000/year, being in the third place as incidence, with a mortality of 880,000 cases (second place regarding the total number of

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deaths induced by cancer) [1]. Age-standardized incidence of CRC rates per sex in Europe ranks this pathology on the third place for both genders [1]. In Romania, CRC is in the second place as incidence after lung cancer, with more than 11,000 new cases every year and a mortality of 6,500/year [1]. This type of cancer is actually the main cause of death in patients with digestive cancers in Romania [2].

The age of developing CRC is decreasing; younger ages seem to be more affected by the disease. In a 10-year surveillance of a national insurance system regarding the new cases with CRC (more than 1,2 million diagnosed in the mentioned period), Moghadamyeghaneh identified an approximately 10% increase of the CRC incidence for patients younger than 65 years and an increase between 9-12% for those under 50 [3]. Fifteen percent of younger patients under the age of 50 years had more advanced stages of CRC compared with older ages [3].

Twenty percent of CRC patients had metastasis at diagnosis [4]. Seven to 26% of patients with localized disease will develop metastasis, and more advanced stages (regional disease) will have 25-44% risk of distant disease [5].

The general prognosis in metastatic colorectal cancer (mCRC), has changed in the last decade, the OS expectancy reached more than 30 months in response to triple-agent chemotherapy regimens combined with targeted therapy [6]. The secret of having good and prolonged survival is to adapt the strategy of treatment in terms of association of drugs, sequences, doses and maintenance therapy for disease, which tends to be chronic, but still remains deadly.

Standard therapy for mCRC is represented by the classical chemotherapy backbone – fluoropyrimidine with oxaliplatin or irinotecan, combined with either anti-EGFR (epidermal growth factor receptor) or anti-VEGF/R (vascular endothelial growth factor receptor) antibodies. Of these agents, bevacizumab is one of the most used.

Guidelines could offer various options for available treatments but cannot answer all the questions raised by clinical situations. One of these issues concerns the available data regarding administration of bevacizumab beyond progression (BYP). Published data of randomised phase 3 trials confirmed the value of this strategy, but the optimal dose of bevacizumab BYP (same dose as in first-line therapy or doubling the dose), remains debatable. In addition to that, bevacizumab has been demonstrated to be an essential component of the maintenance therapy for mCRC. The optimal chemotherapy partner in case of progression for bevacizumab BYP remains less studied (same chemotherapy as induction phase similar to OPTIMOX trials or changing the regimen) [7].

Our study was performed with the aim of adding new information regarding the preferences, strategies and results of clinicians treating of "real life" mCRC patients.

## Methods

*Study's population*

We performed a retrospective consecutive analysis of patients of the Institute of Oncology "Ion Chiricuta" Cluj-Napoca (IOCN) treated for mCRC with bevacizumab and chemotherapy, bevacizumab being continued beyond progression (BYP). The ethics committee of the Institution approved this study. The included patients were stratified according to the dose of bevacizumab BYP – same dose of bevacizumab as for the first-line therapy (SDB) or the double dose of bevacizumab (DDB).

*Inclusion criteria:* age above 18, histological confirmation of CRC, hematological tests with liver & renal functions adequate for chemotherapy, no cardiological contraindication for chemotherapy (including bevacizumab) administration, at least 1 metastatic measurable lesion according to RECIST 1.1 criteria, good performance status (0 to 2), at least 2 months of chemotherapy regimen administration, complete data on treatments and survival.

*Exclusion criteria:* previous administration of bevacizumab or other anti-angiogenic medication; uncontrolled comorbidities, such as hypertension or hypertensive crisis; acute myocardial infarction or unstable cardiovascular disease; gastro-intestinal fistula or bleeding, acute thromboembolism, significant surgical procedure (with a duration of more than 30 min), acute wound trouble of healing, untreated and uncontrolled spinal cord compression or brain metastases, altered performance status, inadequate hematological, hepatic or renal functions.

*Chemotherapy regimens and follow-up*

Chemotherapy regimens used for included patients were: CAPEOX or XELOX – oxaliplatin 130 mg/m$^2$ every 21 days with capecitabine 1000 mg/m$^2$ BID 14 days of 21, FOLFOX 4 – oxaliplatin 85 mg/m$^2$ every 14 days , 5FU 400 mg/m$^2$ bolus and 600 mg/m$^2$ continuous infusion days 1 and 2, folinic acid 400 mg/m$^2$ days 1 and 2, CAPIRI or XELIRI – irinotecan 240 mg/m$^2$ every 21 days capecitabine 1000 mg/m$^2$ BID 14 days of 21, FOLFIRI – irinotecan 180 mg/m$^2$ every 14 days, 5FU 400 mg/m$^2$ bolus and 600 mg/m$^2$ continuous infusion days 1 and 2, folinic acid 400 mg/m$^2$ days 1 and 2. Bevacizumab was administered at 7.5 mg/kg every 21 days in combination with CAPIRI/XELIRI or XELOX/CAPEOX in the first-line and also in the second-line for SDB group of patients, while 15 mg/kg were used in the second-line in the DDB group. For FOLFIRI or FOLFOX regimens bevacizumab was administered at 5 mg/kg every 14 days in the first-line of therapy and in the second-line in the SDB group, or 10 mg/kg in the second-line in the DDB group of

patients. Dose modifications during treatments were according to general recommendations of the guidelines or drug marketing authorities; no dose reduction was done for bevacizumab but delay in administration was allowed in case of toxicity. No significant toxicities in terms of proteinuria or hypertension crisis were noted in the included patients.

After the first-line chemotherapy, most patients underwent maintenance therapy with less aggressive chemotherapy until disease progression or surgical resection. Same or double dose bevacizumab was continued beyond disease progression in combination with a different chemotherapy regimen. All patients were evaluated by CT scan, according to RECIST 1.1.

*Statistics*

OS was defined as the period of time between the first cycle of chemotherapy and death, time-to-treatment failure (TTF) as the period of time between first cycle of chemotherapy and last cycle of second line with bevacizumab (time to second progression), PFS of first-line (PFS 1) – time between first cycle and last cycle of first-line of chemotherapy, PFS of second line (PFS 2) – time between first cycle and last cycle of second line of chemotherapy.

The distribution of patient characteristics (numbers and percentage) was evaluated using $x^2$ test for association. Survival curves were estimated by Kaplan-Meier method, with differences assessed by log-rank test. Cox regression analysis was used to generate hazard ratios (HRs) and corresponding 95% CI. Two-sided p value less than 0.05 indicated statistical significance. All analysis were performed using R version 3.5.1 and Excel 2010.

The items considered of interest were: age, gender, body mass index, type of chemotherapy partner for bevacizumab in first and second-line therapy, dose for each chemotherapeutic agent including bevacizumab, dates for each cycle of chemotherapy and date of death. The main objectives of this analysis were OS, TTF, PFS 1, PFS 2 for both groups – SDB and DDB.

**Table 1.** Patient, treatment and disease characteristics

| *Characteristics* | *DDB (n=40) n (%)* | *SDB (n=111) n (%)* | *p value* |
|---|---|---|---|
| Age (years) | | | |
| Median (range) | 58 (41-77) | 57 (19-75) | |
| Sex | | | 0.69 |
| Male | 24 (60.0) | 62 (58.9) | |
| Female | 16 (40.0) | 49 (44.1) | |
| First-line chemotherapy | | | <0.001 |
| Oxaliplatin-based | 9 (22.5) | 81 (27.0) | |
| Irinotecan-based | 30 (75.0) | 30 (73.0) | |
| Other | 1 (2.5) | 0 (0.0) | |
| Second-line chemotherapy | | | 0.014 |
| Oxaliplatin-based | 20 (50) | 33 (29.7) | |
| Irinotecan-based | 19 (47.5) | 78 (70.3) | |
| Other | 1 (2.5) | 0 (0) | |
| Disease site | | | 0.23 |
| Left | 12 (30.0) | 23 (20.7) | |
| Right | 28 (70.0) | 88 (79.3) | |
| Metastasis localization | | | 0.98 |
| Liver | 30 (62.5) | 91 (58.0) | |
| Pulmonary | 6 (12.5) | 19 (12.1) | |
| Peritoneal | 6 (12.5) | 25 (15.9) | |
| Adenopathies | 2 (4.2) | 6 (3.8) | |
| Bone | 1 (2.1) | 6 (3.8) | |
| Other | 3 (6.3) | 10 (6.4) | |
| Total number of metastasis | 48 | 157 | |
| Average number of metastasis / patient | 1.2 | 1.41 | |
| Number of organs with metastasis | | | 0.13 |
| 1 | 32 (80.0) | 78 (70.3) | |
| 2 | 8 (20.0) | 23 (20.7) | |
| More | 0 (0.0) | 10 (9.0) | |

DDB: bevacizumab double dose, SDB: bevacizumab standard dose

**Table 2.** Chemotherapy regimens depending of the laterality of primary tumor

| *Characteristics* | *All (n=151) n (%)* | *Right sided cancer (n=35) n (%)* | *Left sided cancer (n=116) n (%)* | *p value* |
|---|---|---|---|---|
| Age (years) | | | | 0.80 |
| Under 65 | 123 (81.5) | 28 (80.0) | 95 (81.9) | |
| Over 65 | 28 (18.5) | 7 (20.0) | 21 (18.1) | |
| Median age (range) | 57 (19-75) | 57 (25-74) | 57 (19-75) | |
| Sex | | | | 0.02 |
| Male | 86 (57.0) | 14 (40.0) | 72(62.1) | |
| Female | 65 (43.0) | 21 (60.0) | 44 (37.9) | |
| First-line chemotherapy | | | | 0.12 |
| Oxaliplatin-based | 90 (59.6) | 16 (45.7) | 74 (63.8) | |
| Irinotecan-based | 60 (39.7) | 19 (54.3) | 41 (35.3) | |
| Other | 1 (0.7) | 0 (0.0) | 1 (0.9) | |
| Second-line chemotherapy | | | | 0.05 |
| Oxaliplatin-based | 53 (35.1) | 16 (45.7) | 37 (31.9) | |
| Irinotecan-based | 97 (64.2) | 18 (51.4) | 79 (68.1) | |
| Other | 1 (0.7) | 1 (2.9) | 0 (0.0) | |
| Metastasis - types | | | | 0.18 |
| Liver | 121 (59.0) | 25 (51.0) | 96 (61.5) | |
| Lung | 25 (12.2) | 3 (6.1) | 22 (14.1) | |
| Peritoneum | 31 (15.1) | 12 (24.5) | 19 (12.2) | |
| Adenopathies | 8 (3.9) | 3 (6.1) | 5 (3.2) | |
| Bone | 7 (3.4) | 2 (4.1) | 5 (3.2) | |
| Other | 13 (6.3) | 4 (8.2) | 9 (5.8) | |
| Total number of metastasis | 205 | 49 | 156 | |
| Metastasis – organ involved | | | | 0.27 |
| 1 | 110 (71.9) | 24 (64.9) | 86 (74.1) | |
| >1 | 43 (28.1) | 13 (35.1) | 30 (25.9) | |

## Results

### *Patient characteristics*

Of 694 patients treated with bevacizumab for mCRC in our Institute between 2009-2017, only 162 patients met the criterias for inclusion – bevacizumab BYP. Of these, 11 had bevacizumab BYP in later lines of chemotherapy and were not included in the analysis.

The main characteristics of the included patients are detailed in Table 1.

There were no significant differences between the investigated groups of patients – BSD and BDD, in terms of age, gender, site of primary tumor, types of metastasis and number of organs with metastasis with the exception of the use of oxaliplatin in the first and second-line therapy, which was more frequent in the SDB arm.

Regarding the laterality of primary tumor and other patient characteristics, the left-sided cancer was significantly more frequent in males (Table 2).

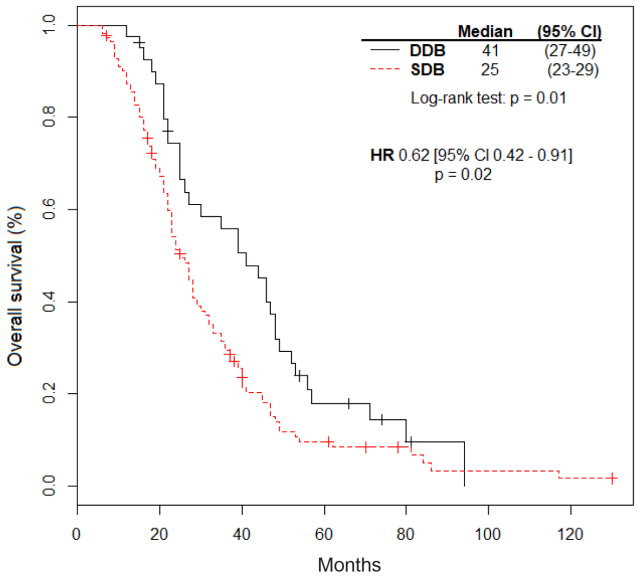


**Figure 1.** Kaplan-Meier survival estimates for patients – overall survival. SDB: bevacizumab standard dose as first-line; DDB: bevacizumab double dose; CI: confidence interval; HR: hazard ratio.

*Survival analysis by dose of bevacizumab beyond progression*

*Overall survival (OS)*

The differences between Kaplan-Meier survival curves were compared by log-rank test. The median duration of survival for the DDB group (treated with a higher dose of bevacizumab) was 41 months compared with 25 months for the SDB group (treated with a lower dose of bevacizumab) (log rank p=0.01). The corresponding HR for death was 0.616 (p=0.0159) (95% CI 0.416-0.913) (Figure 1).

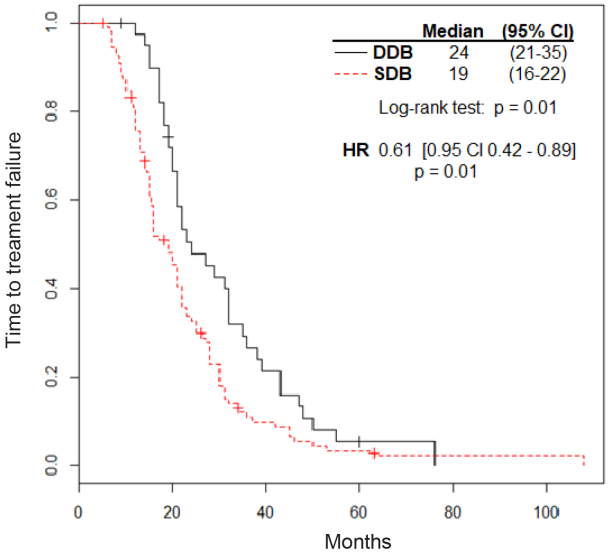


**Figure 2.** Kaplan-Meier survival estimates – time to treatment failure. SDB: standard dose bevacizumab; DDB: double dose bevacizumab; CI: confidence interval; HR: hazard ratio.

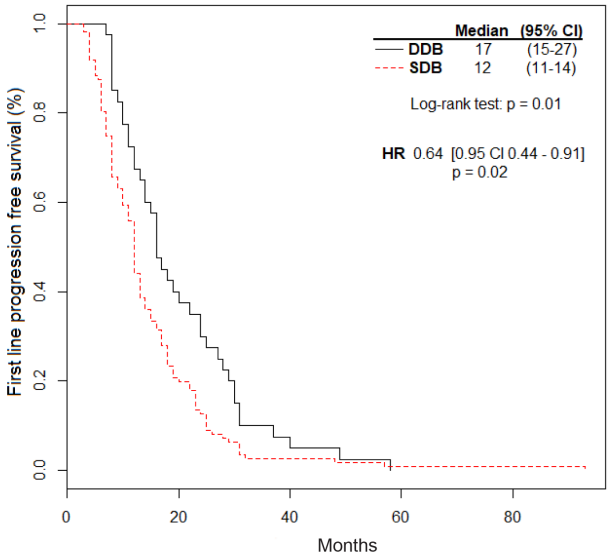


**Figure 3.** Progression-free survival in the first-line treatment (PFS1). SDB: standard dose bevacizumab; DDB: double dose bevacizumab; CI: confidence interval; HR: hazard ratio.

*Time-to-treatment failure (TTF)*

The median TTF (lines 1 and 2) for the DDB group was 24 months compared with 19 months for the SDB group (log rank p=0.009). The corresponding HR for death was 0.6067 (p=0.0985; 95% CI: 0.415-0.886) (Figure 2).

*Progression free survival in the first-line chemotherapy (PFS 1)*

The median PFS in the first-line for the DDB group was 17 months compared with 12 months for the SDB group (log rank p=0.008). The corresponding HR for death was 0.637; (p=0.0157; 0.95 CI: 0.442-0.912) (Figure 3).

Regarding the chemotherapy regimen for bevacizumab-irinotecan or oxaliplatin backbone regimen in the first-line therapy, PFS 1 favored irinotecan associations with statistical significance as shown in Figure 4.

Statistical analysis showed that HR for PFS 1 was 0.687 (95% CI: 0.494 - 0.955, p=0.0255), favoring irinotecan-based chemotherapy.

*Progression free survival in the second-line chemotherapy (PFS 2)*

The median PFS in second-line for the DDB group was 9 months compared with 5 months for the SDB group (log rank p=0.03). The corresponding HR for death was 0.666 (p=0.0369; 95% CI: 0.455-0.976) (Figure 5).

In the second-line therapy no differences in terms of PFS 2 were demonstrated when we compared irinotecan with oxaliplatin-based chemotherapy, with a corresponding HR for death 0.9026 (p=0.563; 95% CI: 0.6379-1.277).

## Discussion

The treatment of patients with mCRC remains one of the most challenging issues. It is well known that only 10-15% of those marginally operable or initially non-surgical patients will become candidates for metastasis resection.

Nowadays, we have multiple chemotherapy regimens options, with different types of toxicities and different impacts on treatment strategies. Despite recent scientific progress in the last decades essential questions still remain.

In daily clinical activities, the oncologist faces some critical issues – and one of them is represented by the associations of systemic treatments which need to be administered in the first-line therapy. These therapeutic schemes are chosen in regard to patients and their physicians' intentions- either conversion to surgery

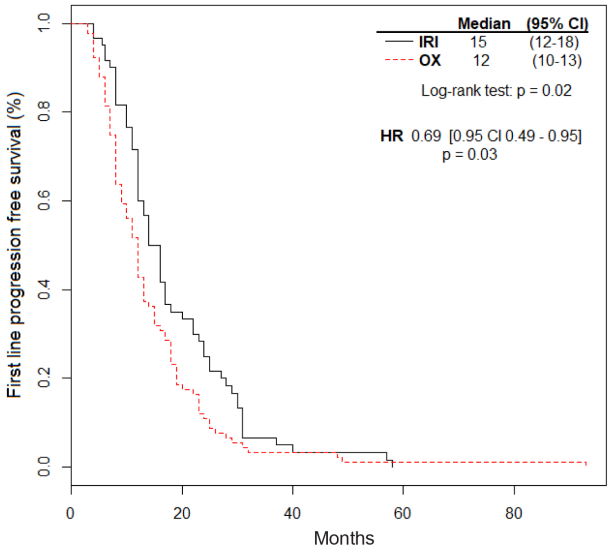


**Figure 4.** Progression-free survival in the first-line treatment (PFS1) depending of chemotherapy combination. IRI: irinotecan-based regimens (FOLFIRI or CAPIRI), OX: oxaliplatin-based regimens (FOLFOX or CAPEOX); CI: confidence interval; HR: hazard ratio.

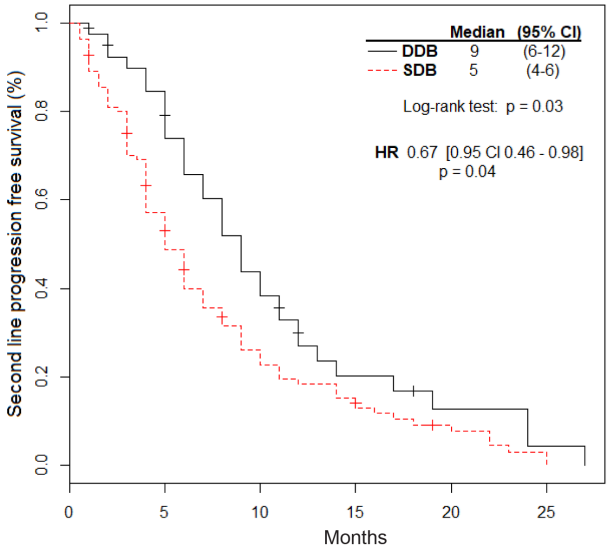


**Figure 5.** Progression-free survival in the second-line treatment (PFS2). SDB: standard dose bevacizumab; DDB: double dose bevacizumab; CI: confidence interval; HR: hazard ratio.

or an increased life expectancy with a tolerable toxicity.

In order to maximize the rate of response it is important to choose in the first-line of therapy the systemic regimens associations with the highest probability to obtain a tumor response. That means for both – classic chemotherapy regimen and biological factors (anti-VEGF/R or anti-EGFR) – the rate of response is the priority. In mCRC patients, FDA and EMA approved both categories of treatments – anti-VEGF (bevacizumab) and anti-EGFR in first- and second-line therapy (anti-EGFR even in third line) [8].

Concerning anti-VEGF vs anti-EGFR therapies– we have data from the published clinical trials FIRE-3 (AIO KRK-0306) [9], the phase II PEAK [10], and CALGB/SWOG 80405 [11]. Their primary endpoints (response rate, PFS or OS) were not met, so for the time being no definite conclusions could be drawn. The chemotherapy partners were either a chemotherapy regimen backbone with irinotecan or oxaliplatin. Little transparencies - if any - were shown concerning the scientific arguments to choose oxaliplatin instead of irinotecan or *vice versa* in addition to a biological treatment in these published trials.

*Timing of traditional chemotherapy: what should be administered first?*

ESMO guidelines recommend the oxaliplatin backbone regimen as the first-line therapy if the case could become operable [12].

Tournigand et al in their randomised study demonstrated that the sequence of oxaliplatin regimen followed by irinotecan-based chemotherapy or the other way around, had similar efficacy in terms of OS, same rate of response (approx. 55%), and PFS1 (PFS until first disease progression), but with different spectrum of toxicities - as more neuropathies and neutropenia occurred in the case of oxaliplatin administration or cardiomyopathies with 5FU [13-15]. Due to these chemotherapy side effects which involve oxaliplatin, especially for neuropathic toxicity which is dose-related and partially reversible, a strategy of "stop and go" was investigated and proved efficient in OPTIMOX-1 trial [7,16].

*Which is the best partner for bevacizumab as first-line treatment for mCRC?*

ESMO guidelines do not outline any clear discrimination regarding the first-line therapy efficacy between both backbone chemotherapy regimens (oxaliplatin or irinotecan) associated to bevacizumab [12].

The CALGB/SWOG 80405 trial which compared anti-EGFR versus anti-VEGF, both combined with chemotherapy regimens in first-line therapy of mCRC, is the only trial conducted as a head-to-head analysis of FOLFIRI versus FOLFOX combined with bevacizumab in 1140 patients. FOLFOX combined with bevacizumab produced a median OS of 26.9 months, compared with FOLFIRI + bevacizumab with a median OS of 33.4 months (no statistical analysis was done in the original trial) [11]. The preferences of investigators for FOLFOX

chemotherapy associated with bevacizumab or cetuximab (73.2%) makes it very difficult to draw definite conclusions [11].

In ARIES, an observational study, Bendell et al analyzed the efficacy of FOLFOX or FOLFIRI combined with bevacizumab in the first-line therapy, in 1211 patients with mCRC. No differences in PFS or OS were observed between arms, although the absolute value OS was superior for FOLFIRI arm (25.5 months) compared with FOLFOX (23.7 months) (not statistically significant – HR: 0.95; 95% CI: 0.78–1.16; p = 0.625) [17]. Due to a higher risk for adverse events linked to classic chemotherapy regimens for the FOLFOX arm, these patients had a more frequent change of the treatment (23.7 vs. 16.2%) compared with FOLFIRI arm [17]. In the ARIES study, both FOLFOX or FOLFIRI seemed to be equal partners for bevacizumab in first-line therapy for patients with mCRC. In real-life conditions, the BEAT study included 1914 patients with mCRC treated with FOLFIRI, FOLFOX or XELOX plus bevacizumab [18]. No statistically significant differences were found neither in terms of PFS between arms (11.6 months for FOLFIRI, 11.3 months and 10.8 months, respectively for FOLFOX and XELOX), nor in OS [16]. The MAVERICC study on 376 patients did not find any differences for OS or PFS between FOLFOX and FOLFIRI in first-line therapy when combined with bevacizumab [19].

In our study patients treated with irinotecan backbone chemotherapy had a statistically significant superiority in OS and PFS compared with oxaliplatin, in first-line therapy but not in second-line treatment, regardless of the dose of bevacizumab (same dose or doubled after disease progression).

In the future the CAIRO 5 trial could offer more accurate data regarding the best partner for bevacizumab treatment in first-line therapy of mCRC patients [20].

*Bevacizumab beyond progression – to double or not the dose?*

Bennouna et al in ML 18147 phase 3 trial, assigned 409 patients (50%) to bevacizumab (2.5 mg/kg per week) plus chemotherapy and 411 (50%) to chemotherapy alone. The study demonstrated a median OS advantage in favour of continuation of bevacizumab beyond disease progression [21]. These findings were confirmed by Masi et al in the smaller BEBYP trial on only 185 included patients, in which PFS and OS supported bevacizumab continuation beyond disease progression [22]. Koeberle et al, in SAKK 41/06 trial, investigated bevacizumab continuation versus no continuation, but failed to demonstrate the non-inferiority of treatment non-continuation vs continuing bevacizumab therapy [23]. CAIRO 3 demonstrated that a continous care in mCRC is better served by bevacizumab administered continously (same dose), either associated or not with 5FU/capecitabine [24].

In a small phase 2 trial, bevacizumab associated with FOLFIRI after progression on a first-line chemotherapy regimen with bevacizumab showed that doubling the dose of bevacizumab led to the same results in terms of PFS and OS as those reported for the second-line combination (without bevacizumab in the first-line) [25].

One of the first evidence in favor of bevacizumab continuation beyond disease progression was given by BRiTE study, where 1445 patients were treated with bevacizumab in first-line therapy and were then treated with or without second-line bevacizumab after progression. Multivariate analysis showed that bevacizumab continuation beyond progression was statistically significantly associated with improved survival (HR, 0.48; p<0.001) [26].

In ARIES observational study, post-progression survival of 1550 included patients was statistically linked to a cumulative dose of bevacizumab after the first progression (p=0.0040) [27]. Same post-progression survival advantage in favor of bevacizumab continuation was found for 573 patients by Cartwright et al [28].

Double dose bevacizumab as second-line of treatment was investigated in ECOG E3200 trial [29]. It was a second-line trial with progression after classic chemotherapy, bevacizumab was not administered truly beyond progression, since it was not part of the first-line treatment. The addition of bevacizumab at a double dose improved PFS, OS and showed a statistically significant response rate.

*Do PFS1, PFS2 or TTF increase the OS?*

These notions were more frequently met in the maintenance treatment strategy in mCRC as defined in CAIRO 3 trial [24]. PFS1 could be inappropriately evaluated due to retreatment periods at disease progression and TTF seems to characterize better the entire treatment efficacy as maintenance therapy. PFS2 is linked mainly to the maintenance period.

Petrelli and Barni showed in 34 randomized clinical trials that OS was better characterized by post-progression survival (PFS2) while each improvement in overall PFS (or TTF) had statistical significance for OS [30].

In our study all items PFS1, PFS2, TTF, OS were in favor of doubling the dose of bevacizumab at progression. An analysis for predictive or prognostic factors is ongoing.

## Conclusions

Our study demonstrates that doubling the dose of bevacizumab at progression could improve OS and time to TTF in patients with mCRC.

Irinotecan could improve the results of systemic association if it is administered in the first-line treatment with bevacizumab.

Available data from published clinical trials need to be reassessed according to tumor microenvironment and Consensus Molecular Subtypes (CMS) classification.

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## Conflict of interests

The authors declare no conflict of interests.

## References

1. Cancer fact sheets. Colorectal Cancer. https://gco.iarc.fr/today/fact-sheets-cancers; 2018 Accessed on May 2019.
2. Vălean S, Armean P, Resteman S, Nagy G, Mureşan A, Mircea PA. Cancer mortality in Romania, 1955-2004. Digestive sites: esophagus, stomach, colon and rectum, pancreas, liver, gallbladder and biliary tree. J Gastrointestin Liver Dis 2008;17:9-14.
3. Moghadamyeghaneh Z, Alizadeh RF, Phelan M et al. Trends in colorectal cancer admissions and stage at presentation: impact of screening. Surg Endosc 2016;30:3604-10.
4. Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 2015;6:38658-66.
5. Edwards BK, Noone AM, Mariotto AB et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014;120:1290-314.
6. Esin E, Yalcin S. Maintenance strategy in metastatic colorectal cancer: A systematic review. Cancer Treat Rev 2016;42:82-90.
7. Tournigand C, Cervantes A, Figer A et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer - a GERCOR study. J Clin Oncol 2006;24:394-400.
8. U.S. Food and Drug Administration. New treatments for colorectal cancer. https://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2004/304_cancer.html; 2004 Accessed on May 2019.
9. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-75.
10. Schwartzberg LS, Rivera F, Karthaus M et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32:2240-7.
11. Venook A, Niedzwiecki D, Lenz HJ et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol 2014;32:abstr LBA 3.
12. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
13. Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-37.
14. Cetean S, Ciuleanu TE, Leucuta DC et al. Hypersensitivity reactions to platinum derivatives: findings of new predictive markers. JBUON 2015;20:1617-23.
15. Cainap SS, Nagy V, Cainap C. Chemotherapy-induced cardiotoxicity in oncology drugs involved and clinical assessment. Farmacia 2016;487-92.
16. Beijers AJ, Mols F, Vreugdenhil G. A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. Support Care Cancer 2014;22:1999-2007.
17. Bendell JC, Bekaii-Saab TS, Cohn AL et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: results from ARIES, a bevacizumab observational cohort study. Oncologist 2012;17:1486-95.
18. Van Cutsem E, Rivera F, Berry S et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol 2009;20:1842-7.
19. Parikh AR, Lee FC, Yau L et al. MAVERICC, a Rand-

omized, Biomarker-stratified, Phase II Study of mFOLFOX6-Bevacizumab versus FOLFIRI-Bevacizumab as First-line Chemotherapy in Metastatic Colorectal Cancer. Clin Cancer Res 2019;25:2988-95.

20. Huiskens J, van Gulik TM, van Lienden KP et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). BMC Cancer 2015;15:365.
21. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013;14:29-37.
22. Masi G, Salvatore L, Boni L et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol 2015;26:724-30.
23. Koeberle D, Betticher DC, von Moos R et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). Ann Oncol 2015;26:709-14.
24. Simkens LH, van Tinteren H, May A et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet 2015;385:1843-52.
25. Kuramochi H, Ando M, Itabashi M et al. Phase II study of bevacizumab and irinotecan as second-line therapy for patients with metastatic colorectal cancer previously treated with fluoropyrimidines, oxaliplatin, and bevacizumab. Cancer Chemother Pharmacol 2017;79:579-85.
26. Grothey A, Sugrue MM, Purdie DM et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008;26:5326-34.
27. Grothey A, Flick ED, Cohn AL et al. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study. Pharmacoepidemiol Drug Saf 2014;23:726-34.
28. Cartwright TH, Yim YM, Yu E, Chung H, Halm M, Forsyth M. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-46.
29. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44.
30. Petrelli F, Barni S. Correlation of progression-free and post-progression survival with overall survival in advanced colorectal cancer. Ann Oncol 2013;24:186-92.
31. Vlad C, Kubelac P, Fetica B, Vlad D, Irimie A, Achimas-Cadariu P. The prognostic value of FOXP3+ regulatory cells in colorectal cancer. JBUON 2015;20:114-9.